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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,757	09/24/2003	Alan Klotz	10211.200-US	4235

25907 7590 02/17/2006

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 02/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/669,757	KLOTZ ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,24,32,36,52,53,60,61 and 130-151* is/are pending in the application.

4a) Of the above claim(s) *53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,24,32,36,52,60,61 and 130-151* is/are rejected.

7)☒ Claim(s) *1,24,32,36,52,61 and 130-151* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response, on December 5, 2005 to the First Action on the Merits of this case mailed August 5, 2005, is acknowledged. It is acknowledged that applicants have cancelled Claims 62-64, 68, 69, 92, 100, 104, 120, 121, 128, and 129, amended Claims 1, 36, 52, 53, 61, and 130, and added Claims 131-151. Claims 1, 24, 32, 36, 52, 53, 60, 61, 130-151 are pending. Claim 53 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 24, 32, 36, 52, 60, 61, and 130-151 are hereby considered.

Objection-Claims

Claims 1, 24, 32, 36, 52, 61, 130-151 are objected to for reciting non-elected subject matter. Applicants are reminded that, in their response of June 28, 2005 (pg 2, parg 2), the following specific invention was elected.

> A polypeptide comprising "the specific combination as follows: (a) a substitution at positions corresponding to positions 144, 193, 198, 201, 218, 223, 227, 228, 229, 230, and 231 of amino acids 25 to 248 of SEQ ID NO: 2) (b) a deletion at positions corresponding to positions 192, 197, and 226 of amino acids 25 to 248 of SEQ ID NO: 2; and (c) an insertion between positions corresponding to positions 224 and 225 of amino acids 25 to 248 of SEQ ID NO: 2." (Examiner's emphasis)

Drawings

Figure 3 is objected to for disclosing sequences that are not identified by a sequence identifier number (SEQ ID NO:). 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences, regardless of whether a given sequence is also embedded in the text of the description or claims of an application. Correction is required.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 24, 32, 36, 52, 60, 61, 130-151 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons. For Claim 1, recitation of the phrase "microbial trypsin" renders the claims indefinite. The Examiner previously assumed, as would one of skill in the art, that said phrase refers to a wild-type trypsin. However, new Claim 145, which recites a microbial trypsin, "wherein the microbial trypsin is a wild-type microbial trypsin", renders the phrase "microbial trypsin" indefinite. It is unclear whether said phrase refers to a wild-type microbial trypsin or some other genus of microbial trypsin molecules. Claims 24, 32, 36, 52, 60, 61, 130-151, as dependent from Claim 1, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reasons. Clarification is required. For purposes of examination, it is assumed, based on Claim 145, that the phrase "microbial trypsin" is meant to mean any wild-type microbial trypsin or any naturally-occurring or recombinant variant thereof having trypsin activity.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claims 1, 24, 32, 36, 52, 61, and 130 under 35 U.S.C. 112, first paragraph, lack of enablement, for the reasons set forth in the prior action, is maintained. In addition, new Claims 131-151 are herein rejected 35 U.S.C. 112, first paragraph, lack of enablement, for the same reasons.

Examiner's note: It is noted that the first and last sentence of the instant rejection in the prior action fails to state that Claim 32 is rejected. However, the reasons for rejection of Claim 32 under 35 U.S.C. 112, first paragraph, lack of enablement, were clearly stated (pg 7, lines 3-9 and pg 7 line 17- pg 8, line 4). It would be obvious to the skilled artisan that the failure to list Claim 32 in the first and last sentence of the rejection in the prior action was merely a typographical error.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(A) An assertion by the Office that the disclosure does not enable the full scope of the recited invention must be supported by evidence or reasoning substantiating the doubts so expressed.

(B) Applicants disclose methods and examples for the construction of variants having chymostrypsin-like activity, wherein the variants are derived from a microbial trypsin, by identifying the position of the amino acids in the microbial trypsin that correspond to the residues of a chymostrypsin responsible for catalytic activity. The residues of chymotrypsin responsible for catalytic activity are well known in the art.

(C) Methods for identifying said residues in microbial trypsins are also known in the art.

(D) The specification describes methods for obtaining microbial trypsin-like proteins.

(E) As of the filing date, it was routine to produce and screen hundreds of thousand of mutant sequences.

(F) Hedstrom et al, 1992 disclose the engineering of a trypsin gene to encode a polypeptide with chymostrypsin activity.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: The reasons that the full scope of the recited invention is not enabled by the specification are set forth in the prior action. In short, the specification does not enable the skilled artisan to make and use the full scope of all variants of any microbial trypsin, wherein the variant has chymotrypsin-like activity and has, relative to SEQ ID NO: 2, a substitution at one or more of residues corresponding to 144, 193, 198, 201, 218, 223, or 227-231, a deletion at one or more of residues corresponding to 192, 197, or 226, an insertion between residues 224 and 225, and has either 70% homology to residues 25-248 of SEQ ID NO: 2 or hybridizes at low stringency to residues 202-801 of SEQ ID NO: 1.

Further explanation for why the scope of said invention is not enabled is herein provided. The number of polypeptides encompassed by the phrase "a microbial trypsin" is extremely large, including both any wild-type microbial trypsin and any naturally-occurring or recombinant variant thereof having trypsin activity (as described above for the rejection under 35 USC 112, second paragraph). It would be undue experimentation for the skilled artisan to isolate and test all said variants for trypsin activity. Even if said isolating and testing were not undue, which it is, it is more likely than not that all said " microbial trypsins" could not be

successfully aligned with SEQ ID NO: 2 in a manner to identify residues corresponding to 144, 192, 193, 197, 198, 201, 218, 223-225, and 226-231.

The full scope of the invention requires further undue experimentation to identify and test, for chymotrypsin activity, all polypeptides having the designated substitutions, deletions, and insertion and either at least 70% homology to residues 25-248 of SEQ ID NO: 2 or hybridizes at low stringency to residues 202-801 of SEQ ID NO: 1. The genus of said polypeptides is extremely large and to make and test all said polypeptides is clearly undue experimentation. Guo et al, 2004 show that the percentage of active mutants for multiple mutations appears to be exponentially related by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced (Table 1). Applying this estimate to the protein recited in the instant application, 70% identity allows up to 68 mutations within the 224 amino acids of residues 25-248 of SEQ ID NO: 2 and, thus, only $(.66)^{68}$ X 100% or 5.3×10^{-11}% of random mutants having 70% identity would be active, i.e. 1 out of $1.8 \times 10^{+12}$ mutants. Current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants, despite even this being an enormous quantity of experimentation that would take a very long time to accomplish. But finding a few mutants within several billion or more, as in the instant claims, would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Sufficient guidance has not been provided in the instant specification.

(B) Reply: As stated in the prior action, it is acknowledged that recombinant methods for altering the structure of proteins as well as methods for testing for tyrpsin and chymotrypsin activity are known in the art. However, because the scope of the instant claims encompass an extremely large number of proteins, to make and test all said proteins for the desire activity would require undue experimentation (see (A) above).

(C) Reply: It is acknowledged that methods for aligning two or more proteins are known in the art. However, as described in (A) above, the skilled artisan would believe, it is more likely than not, that all said " microbial trypsins", including all wild-type and variants thereof, could not be successfully aligned with SEQ ID NO: 2 in a manner to identify residues corresponding to 144, 192, 193, 197, 198, 201, 218, 223-225, and 226-231.

(D) Reply: See (A) and (C).

(E) Reply: See (A).

(F) Reply: It is acknowledged that Hedstrom et al, 1992 enables the skilled artisan to convert bovine trypsin to a protein having chymotrypsin-like activity by replacing in bovine trypsin loops or residues 185-188 and 221-225 with the analogous loops in chymotrypsin. However, for the reasons set forth in the prior action and above, neither the specification nor the prior art, including Hedstrom et al, 1992, enable the skilled artisan to make and use the full scope of the recited invention.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that Applicants identify support, within the original application, for any amendments to the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
Art Unit 1656

SHERIDAN SWOPE, Ph.D.
PATENT EXAMINER